REMARKS/ARGUMENTS

Applicants thank Examiner Dunston for the helpful telephonic interview held on February 17, 2010 and February 24, 2010, in which the instant amendments to the claims were discussed. Applicants have added the gene name language as discussed with Examiner Dunston in order to further prosecution and help address the outstanding enablement and written description-based rejections.

The Office has expresses concerns regarding detection of EST ID 32f4 and hoxA7 by any means other than using oligonucleotide probes on an ordered array. This concern arises from the fact that Applicants TaqMan experiments (used to confirm the array results) did not detect EST ID 32f4 and detected no significant change in the level of hoxA7 between control and test samples (i.e., the hoxA7 TaqMan results did not confirm the array results).[1]

I) Detection of levels of EST ID 32f4

Enablement

The Office has previously alleged that the claims are not enabled because the application allegedly does not disclose sufficient information to allow a skilled artisan to detect EST ID 32f4. The application does not disclose the sequences of the probes found on the HG-u95av2 Affymetrix microarray that allow detection of EST ID 32f4. Apparently, this alone would not render the claims non-enabled, since the application also does not disclose the probes on the HG-u95av2 array that allow detection of any of the other genes recited in the claims. Instead, the Office believes that a skilled artisan is not taught how to detect the level of expression of EST ID 32f4 because the application (and corresponding Scherer et al. publication [of record]) indicate that the inventors did not successfully design primers to EST ID 32f4 for use in a confirmatory TaqMan Q-PCR experiment due to limited sequence information for EST ID 32f4. The Office has argued that this evidences unpredictability as to whether a skilled artisan would be able to design primers to detect the level of expression of EST ID 32f4. The Office concludes that there is insufficient information in the application to teach a skilled artisan how to detect the level of expression of EST ID 32f4, and therefore the claims lack enablement and a written description.

The Office is mistaken in this conclusion for the following reasons.

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[1] Applicants note that the TaqMan results were merely used for confirmation of the array results. Thus, Applicants believed that TaqMan confirmation of 8 of the 10 genes in Table 3 was sufficient to show that the genes of Table 3 were differentially regulated between control and test samples. Indeed, this 80% confirmation was sufficient to gain publication of the results in the peer-reviewed article Scherer et al. (2003) Transplantation 75:1323 [of record].

I) Applicants are not Required to Disclose the Sequences of Probes on the HG-u95av2 Array that Allow Detection of EST ID 32f4.

The HG-u95av2 Array is a commercially available reagent that one may use to in performing the instant methods. That reagent was available at the time of filing – and that reagent is still available.[2] Upon reading the instant application, a skilled artisan would be able to:

a) purchase the HG-u95av2 array from Affymetrix;
b) use that array to interrogate control and test samples for, in the case of the instant claims, the level of expression of the genes recited in the instant claims;
c) compare the levels of expression of the genes recited in the instant claims; and
d) based on that comparison, diagnose chronic rejection.

There is no undue experimentation undertaken when following these simple steps – all of which Applicants themselves performed and have set forth in great detail in the Examples. The Office argues that in order to enable the instant claims, Applicants are required to describe how the HG-u95av2 array is capable of identifying EST ID 32f4, i.e., the sequences of the probes that detect EST ID 32f4. Applicants respectfully disagree. The HG-u95av2 array is merely a commercially available reagent useful in the instant methods. Biotechnology patent applications often disclose the use of various commercially available reagents (e.g., Primer Express software, TRITON-X, RNEASy columns, QUIAQUICK kits, MEGASCRIPT kits, BIOROBOT workstations, etc.) used to perform steps in a claimed method, but an applicant is not required to detail the formulation or structure of those reagents. Similarly, Applicants are not required to detail the "formulation" of the HG-u95av2 array, as long as this array was readily available to the public at the time of filing.[3] This principle was discussed in *In re Metcalfe*, 56 CCPA 1191, 1196 (CCPA 1969). In *Metcalfe*, an applicant had recited certain resins useful in preparing a claimed composition by their trade name. During prosecution, the applicants submitted commercial pamphlets that had been available in Australia at the time of filing to show the particular properties of those resins. On appeal, the Board stated that a skilled artisan could not decide from the properties in the commercial pamphlets whether the resin would be effective a performing the desired function in the claimed composition. The CCPA stated

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[2] The probe sequences on the HG-u95av2 array do not change over time. The probes present on an HG-u95av2 array purchased in 2000 are the same probes that are present on an HG-u95av2 array purchased in 2010. While the sequences interrogated could change (as evidenced by the quarterly update of the annotation files for Affymetrix arrays) –the probes on a given HG-u95av2 array do not change.

[3] Applicants note that the HG-u95av2 array is also readily available today.

> when, in a working example, an applicant identifies a material (here a resin) as being useful in the practice of his invention, it is unnecessary for the worker skilled in the art to redetermine the usefulness of that material in the disclosed invention. Here, for instance, appellants' specification says, in effect: to practice this invention, use these general materials in these specific proportions and, as examples, these are some resins that work. With respect to the examples, there is nothing left for the worker in the art to determine.

As with the resins disclosed by commercial name in *Metcalfe*, so too does Applicants' disclosure of the Affymetrix array leave nothing for the worker to determine.

MPEP 2164.01 also discusses enablement in the context of whether a starting material or apparatus used to make a claimed invention is available – and expresses concerns about satisfying the enablement requirement if a claimed process requires a particular organism or apparatus. The MPEP suggests that, at least according to *In re Ghiron*, 442 F.2d 985 (CCPA 1971), an applicant must provide sufficient details of a particular apparatus required to perform a method if the apparatus **was not** readily available. The *In re Ghiron* holding has been confirmed by the Federal Circuit in *Med. Instrumentation & Diagnostics Corp. v. Elekta AB*, 344 F.3d 1205, 1224 (Fed. Cir. 2003) (stating that software that is commercially available or within the skill of ordinary practitioners need not be included in the specification). The concept of *In re Ghiron* (i.e., an applicant need not disclose details about subject matter that a skilled artisan can readily obtain or ascertain) has been applied to biotechnology inventions. MPEP 2404.01 states:

> In an application where the invention required access to specific biological material, an applicant could show that the biological material is accessible because it is known and readily available to the public. The concepts of "known and readily available" are considered to reflect a level of public accessibility to a necessary component of an invention disclosure that is consistent with an ability to make and use the invention.

See also *In re Wands*, 858 F.2d 731 (Fed. Ciir. 1988) (stating "[a]lthough inventions involving microorganisms or other living cells often can be enabled by a deposit, ... no deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation). The instantly claimed subject matter does not present an *In re Ghiron* situation, since the HG-u95av2 chip **was** known (e.g., artisans were aware that there existed an Affymetrix array capable of measuring the level of EST ID 32f4) and readily available (i.e., the HG-u95av2 was on sale by Affymetrix) at the time of filing. Accordingly, neither of the exceptional criteria (a process requiring an unavailable apparatus or a process requiring an unavailable organism) set forth in the MPEP that trigger *In re Ghiron* are met. A skilled artisan need not know details of the HG-u95av2 array in order to use that array. It simply does not matter by which probes the HG-u95av2 array works to detect EST ID 32f4 – it is only important that the HG-u95av2 array, which was known and readily available at the time of filing, does detect levels of EST ID 32f4.

For this reason, please withdraw the outstanding enablement-based rejection of the claims.

II) The Sequences of the Probes on the HG-u95av2 Array that Allow Detection of EST ID 32f4 were Available at the Time of Filing.

The Office emphasizes that "the Affymetrix 31377_r_at probe set was not well known in the art at the time the invention was made." (Advisory Action at page 4). This is because the Office could not find the term "31377_r_at" in a search of PubMed, Google Scholar and EAST. The Office concludes that "the probe sequences do not appear to have been available in a printed publication prior to the effective date of the present application. Furthermore, the presence of the sequences in an online database cannot substitute for the disclosure of the sequences when the sequences are essential to the practice of the claimed invention." *(Id.)*.[4]

The test for enablement set forth in MPEP 2164.01 is whether the disclosure, coupled with information known in the art, would teach a skilled artisan how to make and use a claimed invention. Because the enablement standard considers that which is already available to skilled artisans, a patent application need not disclose details or information that is already well known. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); accord *In re Wands*, 858 F.2d 731 (Fed. Ciir. 1988); *accord Capon v. Eshar*, 418 F.3d 1349 (Fed. Cir. 2005). The probe sequences found on the HG-u95av2 Array were available to the public for download from the Affymetrix website in document form prior to Applicants' filing date. As such, even if the probe sequences useful to detect EST ID 32f4 were "essential to the practice of the claimed invention" (and Applicants submit that they are not) – those probe sequences were readily available to the public at the time of filing the instant application. The fact that the probes were downloadable from the Affymetrix website, rather than found, e.g., in a journal article, is not relevant.[5]

For this reason, please withdraw the outstanding enablement-based rejection of the claims.

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[4] The enablement standard does not require that knowledge available to a skilled artisan must be found in a "printed publication" – nor does it exclude knowledge available as part of a public database. If the Office is aware of some passage from the MPEP, or a decision from the Board or a court that limits knowledge to printed publications (and excludes databases and commercial material), Applicants respectfully request the Office to provide that reference.

[5] See *In re Metcalfe*, 56 CCPA 1191, 1196 (CCPA 1969) ("[s]ection 112 simply requires that a disclosure of an invention enable any man skilled in the relevant art to make and use it. No mention of convenience is made; thus, even if the origin of the material is in Australia, this is merely a matter of degree of convenience and not a matter of lack of availability.")

III) A Skilled Artisan Could Readily Design Probe and Primer Sequences to Detect EST ID 32f4 at the Time of Filing.

The Office agrees that a skilled artisan would be able to use the available EST ID 32f4 sequence from GenBank in combination with known techniques or computer programs to design primers and probes to the sequence of EST ID 32f4 – but the Office argues that the ability of those primers and probes to function is unpredictable. (Advisory Action at pp. 5-6). The Office bases this alleged unpredictability on Applicants' corresponding publication (Scherer et al, of record), in which the disclosed TaqMan probe/primer set did not work to detect the level of expression of EST ID 32f4. (Advisory Action at p. 5).

The standard for enablement is not "unpredictability".[6] Enablement is a multi-faceted analysis that considers many factors, only one of which is the level of predictability in a particular field. A proper analysis of whether any experimentation is undue requires an analysis of *all* of the pertinent *Wands* factors. (MPEP § 2164.01(a))(emphasis added). It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. (*Id.).* Factors besides predictability include the nature of the invention, the state of the prior art, and the level of one of ordinary skill in the art. For the instant claims, the level of ordinary skill is quite high – i.e., detection of nucleic acid sequences has been practiced by molecular biologists for decades. The nature of the invention is not complex – i.e., the claims simply require analysis of particular nucleic acid levels in selected samples, a comparison of those levels, and a diagnosis based on that comparison. The state of the prior art provides extensive teachings of how to design and test primers for their ability to detect the level of a given nucleic acid. (see pp.9-10 in Amendment and Response, filed January 11, 2010). These *Wands* factors weigh strongly for the enablement of the instant claims.

The Office asserts that because Applicants primer set did not work in the TaqMan assay, there is "no convincing evidence on the record that one could design primers and probes that function to reliably detect expression of W26469 to assess the risk of chronic rejection." (Advisory Action at p. 6). *How can this be?* Extremely convincing evidence that a skilled artisan could design primers and probes that reliably detect expression of EST ID 32f4 exists in the HG-u95av2 array. This array has 12 different probes that detect EST ID 32f4. This array, with those same 12 probes, was available at the time of filing the instant application. Thus, at the time of

[6] The unpredictability of the science is relevant to deciding how much experimental support is required to adequately describe the scope of an invention. *Capon*, 418 F.3d 1349 (Fed. Cir. 2005). However, the enablement standard asks if the particular amount of experimentation required is undue. Thus, the other *Wands* factors must also be considered.

filing, a skilled artisan (i.e., Affymetrix) very clearly had already designed probes capable of reliably detecting expression of EST ID 32f4. While Applicants TaqMan primer/probe set did not successfully detect EST ID 32f4 levels – the Affymetrix 31377_r_at probe set did successfully detect EST ID 32f4 levels. Thus, the HG-u95av2 array is uncontroverted evidence that probe and primer construction for detecting the level of expression of EST ID 32f4 is not unpredictable.

Even if Affymetrix had not already designed probes that reliably detect EST ID 32f4, Applicants submit that the experimentation required for a skilled artisan to design primers and probes useful for detecting expression of EST ID 32f4 would not be undue; rather, it would merely be routine trial and error. At the time of filing, Applicants designed TaqMan primers using Applied Biosystem's Primer Express 1.0 version software. The primers suggested by that particular software for use in the particular assay of choice (i.e., TaqMan RT-PCR) did not work. However, this is not evidence that a different software system would not have designed useful primers. This also does not mean that the TaqMan assay using the Primer Express 1.0 probes could not have been optimized by routine trial and error to detect expression of EST ID 32f4 (see previous response at pp. 9-10 and the documents cited therein that describe the routine, trial and error optimization used to design primers). Moreover, the TaqMan assay has very particular probe criteria that one must satisfy (see, e.g., p. 16 of the filed application). As such, while a TaqMan assay may not work as an expression detection system for EST ID 32f4, this does not indicate that alternative expression detection system (e.g., SYBRgreen real-time RT-PCR, classical semi-quantitative RT-PCR, or Northern blotting) would not be useful. The Office provides no evidence of the "unpredictability" in measuring levels of EST ID 32f4 *except* that Applicants did not successfully do so using Applied Biosystem's Primer Express 1.0 version software and a TaqMan assay.[7] All that can be derived from Applicants' lack of success using the EST ID 32f4 primers suggested by the Primer Express 1.0 version software in the TaqMan assay is that Applicants decided not to invest extra time and money to build a custom TaqMan assay by trial and error or to use alternative expression detection. And why would Applicants waste this time and money – when a perfectly good and commercially available HG-u95av2 array could be purchased?

As previously stated, various computer algorithms available at the time of filing would produce dozens of potential primers and probes – and a skilled artisan need only purchase and test those probes and primers in, e.g., a PCR reaction, to identify those that functioned. This testing, while repetitive, is neither complex, nor is it unreasonable. The routine optimization

[7] Notably, Scherer et al. state that "the known DNA sequence was insufficient to design functional TaqMan primer-probe sets." Scherer et al. does not state that the known DNA sequence for EST ID 32f4 was insufficient to design ANY functional primer / probe set, a primer set, or even a probe. There are dozens of other techniques useful for expression analysis – and the Office has provided no evidence that these other techniques would not be useful.

required to strike upon an ideal hybridization probe/primer and condition is not undue, nor is it even burdensome. It is a standard molecular biology concern that is successfully addressed in thousands of molecular biology laboratories every day. In fact, a skilled artisan would be expected to have success in designing EST ID 32f4 probes, as evidenced by Affymetrix' success in EST ID 32f4 probe design. Indeed, running the EST ID 32f4 nucleic acid sequence thorough a version of Primer3[8] available at the time of filing the instant application produces several sets of primers and one potential probe. (See Appendix A and Appendix B). Notably, the probe identified by Primer3 (designated by the symbol "^") has 19 nucleic acids found in one of the 25 nucleic acid-probes in the Affymetrix 31377_r_at probe set (shown underlined in Appendix B; see also page 8 of the Amendment and Response, filed January 11, 2010). Thus, using only a single algorithm (i.e., Primer3) available at the time of filing, a skilled artisan would likely have identified a probe for detecting the level of expression of EST ID 32f4.

Finally, even if one were not able to use a traditional 20-25 base pair primer designed from the GeneBank sequence given to measure the level of EST ID 32f4 – one could employ the known portion of the EST ID 32f4 sequence (about 340 nucleotides, see underlined portion of W26469, below) to obtain high specificity in hybridization-based expression analysis techniques.

W26469

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NNNNNNNNNNNNTNNTNNNNCGGNGGNCTACCCTNCATACTTAGTTGTGAGATCCATCCC
CTGGCTTCATTCCCTGAACTGGCTTTAGNAACNCTGGCAGTCTAGCTTATAACCCCCAGG
CTGACTAGAGAACTCAAGGTAAAAGCAGCCCAAGAAAAACAGACCAACAGAAAAGCAATG
AGAGAAAGGATGAAGGTTCCCTNCTCGATGATCCATTAANTGGAAGAGTAACCCAAGAAA
ACATCATGGANTCCAAGANTCAGTGGATCCAGCACAANAAGGNGGNAAAGGGNNATTCAG
CTNGGTCTTANCAGGTGACTGTCAAANNNNGGNNTNNNCCCAGNNTGNNCTGNTCAANNN
NNNTNNNNCAGNNTNNNNTNGNCANNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
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NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNGG
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This large stretch of nucleotides would be expected by a skilled artisan to function as a highly specific hybridization probe for EST ID 32f4. This argument was presented in the previous response, but the Office has not yet answered this position. Instead the Advisory Action focuses only on the TaqMan assay that did not work. But what of this 340 nucleotide probe for a hybridization assay? The Office has not provided any evidence or argument why this would not be expected to work. According to MPEP 707.07(f), the Office must take note of an applicant's argument and answer the substance of it. Therefore, Applicants respectfully request the Office

[8] Applicants ran the sequence using the Primer3 default settings. See Appendix A.

to provide explicit reasoning why a skilled artisan would not believe that the above underlined portion of EST ID 32f4 could not be used in hybridization analysis, e.g., a Northern blot.

As described above, no undue experimentation is required to detect the level of expression of EST ID 32f4. For at least the above reasons, Applicants respectfully submit that the claims are enabled.

Written Description Rejection

The Office's written description rejection is also based on recital of EST ID 32f4 in the pending claims. For the following reasons, that rejection is respectfully traversed.

The Office is concerned that the structure of EST ID 32f4 is not sufficient to allow one to envision the structure of a reagent useful to assay the level of EST ID 32f4 in order to perform the claimed methods. To satisfy the written description requirement, Applicants need only "reasonably convey" sufficient characteristics so that a skilled artisan can "visualize or recognize the identity" of the invention. *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985); *Regents of the University of California v. Eli Lilly, Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). As described above in the enablement section, in order to detect the level of expression of EST ID 32f4, a skilled artisan need only purchase the HG-u95av2 array, download the probe data for the HG-u95av2 array (which was available from Affymetrix at the time of filing the instant application) or look to GeneBank to recognize that Applicants possessed the currently claimed methods. More specifically, the HG-u95av2 array is known to be useful to detect the level of expression of EST ID 32f4, the sequence of the probes that detect EST ID 32f4 on the HG-u95av2 array were available to the public at the time of filing, and there is adequate evidence that the nucleotide sequence available for EST ID 32f4 is sufficient to allow a skilled artisan to design probes and primers useful in various techniques to measure the level of EST ID 32f4 in a sample from a patient. Accordingly, the specification reasonably conveys that Applicants possessed the claimed methods, and a skilled artisan would recognize the same. For at least these reasons, Applicants respectfully submit that the claims are adequately described.

II) Detection of levels of hoxA7

Enablement

The reported results in the specification for hoxA7 TaqMan simply means that Applicants had either a non-optimal or a non-functional TaqMan assay primer probe set. The slight upregulation of hoxA7 in the Q-PCR with +1.86 is not significant (below 2.0), while the Affymetrix chip result shows a significant downregulation of hoxA7 (-5.03). A skilled artisan would

understand there to be a problem in the hoxA7 TaqMan assay[9] since the TaqMan hoxA7 results were not significant, but the other confirmatory TaqMan assays (except the EST ID 32f4 TaqMan correlated to the array results) did correlate with the chip results. With Q-PCR assay optimization, the discrepancy could have been resolved, even in 2002. However, a Q-PCR confirmation success rate of 80% overall (8 out of 10 genes) was enough to convince Applicants (and the journal *Transplantation*, in which Applicants' results were published) of the validity of the method. Thus, TaqMan optimization (or detecting hoxA7 via another method, e.g., SYBRgreen real-time RT-PCR, classical semi-quantitative RT-PCR, or Northern blotting) was not undertaken by Applicants.

At the time of filing the instant application, there was one known sequence for hoxA7 – which was found in both GenBank (AJ005814) and RefSeq (NM_006896). The Affymetrix probe set 40343_at on the HG-u95av2 array comprises 497 base pairs of a cluster including AJ005814 (GenBank's human hoxA7 sequence). The first 880 base pairs of AJ005814 included the translated open reading frame – and the matching Affymetrix probe set. This portion of AJ005814 is identical to the current curated RefSeq sequence NM_006896. However, the remaining 3' untranslated regions of GenBank and the current curated RefSeq sequence NM_006896 are different. Unfortunately, it is within the divergent 3' portion that Applicants designed TaqMan primer probe sets (the TaqMan assay provided for hoxA7 in the specification was designed around position 1620 of the GenBank sequence for hoxA7). As a result, the Q-PCR assay likely did not interrogate the same sequence as that interrogated by Affymetrix probe set 40343_at. In sum, the TaqMan assay in the specification likely did not interrogate hoxA7.

Because of the presence of unknown sequence in the 3' end of the GenBank hoxA7 sequence, which resulted in Applicants' TaqMan assay not detecting hoxA7, the Office is concerned that other skilled artisans could make the same mistake in their PCR or hybridization techniques. The Office contends that it is unpredictable whether a skilled artisan would be able to measure the level of expression of hoxA7 by any method other than using the HG-u95av2 array.

First, as noted above – "predictability" is only one of the Wands factors. Factors besides predictability include the nature of the invention, the state of the prior art, and the level of one of ordinary skill in the art. For the instant claims, the level of ordinary skill is quite high – i.e., detection of nucleic acid sequences has been practiced by molecular biologists for decades. The nature of the invention is not complex – i.e., the claims simply require analysis of particular

[9] A gene chip and quantitative PCR assay generally provide consistent results (at least in the direction of differential gene expression, i.e., upregulated genes stay upregulated and vice versa, with effects in Q-PCR often being more pronounced).

nucleic acid levels in selected samples, a comparison of those levels, and a diagnosis based on that comparison. The state of the prior art provides extensive teachings of how to design and test primers for their ability to detect the level of a given nucleic acid. (see pp.9-10 in Amendment and Response, filed January 11, 2010). These *Wands* factors weigh strongly for the enablement of the instant claims.

Second, Applicants respectfully submit that the Office's concern is misplaced. It is clear from the results that the TaqMan assay for hoxA7 did not mimic the array results. As a result, a skilled artisan, understanding that the array and TaqMan assay results should correlate, would have either investigated the disclosed hox7A primers further or would have simply designed a different set of hoxA7 primers/probes. If that artisan chose to investigate further, that artisan could BLAST Applicants' TaqMan primer set to determine whether there is any cross reactivity with other mRNAs or ESTs. Indeed, such a BLAST performed against RefSeq_RNA today identifies a portion of human SERTAD2 mRNA and human fucosyltransferase 6 with significant homology to Applicants' TaqMan primers. SERTAD2 was also picked up as a potential target using Primer Blast. In addition, a BLAST with Applicants' TaqMan primers performed against the NCBI EST database identified six human ESTs that are potential targets for Applicants' TaqMan primers. In any case, a skilled artisan, noting that Applicants' TaqMan results for hoxA7 did not mimic the array results, would select a different position of the hoxA7 sequence for interrogation.

The art available before Applicants' priority date is replete with examples of techniques that a skilled artisan could use to identify the expression level of hoxA7. For example, the probe set on the HG-u95av2 array interrogates the open reading frame of hoxA7. So too could a skilled artisan interrogate the open reading frame of hoxA7 with primers and probes. A skilled artisan would also be able to select one of the many art recognized primers and probes useful for measuring the expression level of human hoxA7. A brief search of PubMed for articles published before Applicants' August 2002 priority date identified numerous articles from various authors that employed many techniques to measure hoxA7 expression. The following (non-exhaustive) list provide examples of techniques used to measure human hoxA7 expression:

Naora et al. (2001) PNAS 98:15209-15214;
Afonja et al. (2000) Leukemia Res. 24:849-855;
Kim et al. (2000) Molecular Biotech. 14:19-24;
Drabkin et al. (2002) Leukemia 16:186-195;
Calvo et al. (2000) PNAS 97:12776-12781;
Adjaye et al. (2000) Mol. Hum. Reprod. 6:707-11;
Stelnicki et al. (1998) J. Invest. Dermatol. 110:110-115.

These papers are submitted herewith as part of an Information Disclosure Statement. They provide direct evidence that measuring the level of nucleic acid expression of hoxA7 is not unpredictable and a skilled artisan would be able to do so without any undue experimentation.

In sum, Applicants' confirmatory primer/probe set was unfortunately chosen to interrogate a portion of the GenBank hoxA7 deposit that probably does correlate to hoxA7. However, given the level of success of others, the state of the prior art, and the level of skill in the field, the claimed subject matter is enabled. A skilled artisan would note the discrepancy in the array and TaqMan results and would simply select a different set of primers and probes (either designed *de novo* or selected from the available literature) to detect hoxA7 expression. As a result, the claims, as they relate to measuring the level of expression of hoxA7 are enabled and adequately described.

CONCLUSION

In light of the above amendments, observations and remarks, Applicants respectfully submit that the presently claimed invention satisfies 35 U.S.C. §112, and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims in this application is earnestly solicited.

Applicants' undersigned attorney may be reached in our New Jersey office by telephone at (862) 778-9308. All correspondence should continue to be directed to our below-listed address.

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